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Date: October 16, 2001
To: Examiner Lisa Cook
Facsimile No.: 703-746-5216
From: Donna Macedo, Assistant to Bret Field
Re: Interview Agenda for 09/716,054

Message: See attached for details

Total number of pages, including this cover sheet: 25

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INTERVIEW AGENDA

STAN-166 Crabtree et al. 09/716,054 Bifunctional Molecules and Their Use in the Disruption of Protein-Protein Interactions	October 17, 2001 10:30 AM Examiner Lisa Cook Fax 202 703 305 0808 Art Unit 1641
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See Response filed on October 3, 2001

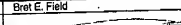
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P. 03

AMENDING CLAIMS


See Response filed on October 3, 2001

CERTIFICATE OF MAILING							
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.							
Name (Print/Type)	Donna Macedo		Signature	<i>D. Macedo</i>		Date	10-30-2001
TRANSMITTAL <input type="checkbox"/> Small Entity <input checked="" type="checkbox"/> Large Entity				Application Number	09/716,054		
				Confirmation Number	N/A		
				Filing Date	November 17, 2000		
				First Named Inventor	Crabtree		
				Examiner	Lisa V. Cook		
				Group Art	1841		
				Attorney Docket No.	STAN166		
ENCLOSED:		Claims	No. of claims as filed or after amendment	Most claims previously paid for	# Extra Claims	Rate	Totals
<input checked="" type="checkbox"/> Amendment Under Rule		Total	27	26	1	18	\$ 18.00
<input checked="" type="checkbox"/> 37 CFR § 1.111		Independent	3	3	0		\$ -
<input checked="" type="checkbox"/> Pages 18		Multiple					\$ -
		Total Extra Claim Fees					\$ 18.00
<input type="checkbox"/> Applicant's Petition for an Extension of time from _____ to _____				A _____ month extension was previously filed and paid for thereby reducing the basic fee.			
<input type="checkbox"/> Response to File Missing Parts (with copy of formalities letter)				Fee _____ Surcharge Fee _____ Fee _____ Fee _____ Fee _____ Subtotal \$ -			
<input type="checkbox"/> Information Disclosure Statement				Fee _____ Subtotal \$ -			
<input type="checkbox"/> PTO Form 1449				Pages _____			
<input type="checkbox"/> Copies of Cited References				Pages _____			
<input type="checkbox"/> Other				Fee _____ Subtotal \$ -			
<input type="checkbox"/> Response to Notice to Comply (with copy of Notice to Comply)				Fee _____			
<input type="checkbox"/> Sequence Listing Certification				Pages _____			
<input type="checkbox"/> Paper Copy of Sequence Listing				Pages _____			
<input type="checkbox"/> Diskette in computer-readable format				Fee _____			
<input type="checkbox"/> Other				Fee _____			

<input type="checkbox"/> Terminal Disclaimer		Fee	
<input type="checkbox"/> Appeal to Board of Appeals and Appeal Communication to Group			
<input type="checkbox"/> Notice of Appeal	Pages		Fee
<input type="checkbox"/> Appeal Brief in Triplicate	Pages		Fee
<input type="checkbox"/> Reply Brief	Pages		Fee \$ -
			Subtotal \$ -
<input type="checkbox"/> Other Enclosures and/or Fees		Fee	
<input type="checkbox"/> Change of Correspondence Address		TOTAL FEES \$19.00	
<input checked="" type="checkbox"/> Return Receipt Postcard			
<p>The Commissioner is authorized to charge any fees which may be required, or credit any overpayment to Deposit Account 50-0815. If additional fees are required, including extensions of time, please consider this a petition therefore. A duplicate copy of this transmittal is enclosed.</p>			
SIGNATURE OF APPLICANT, ATTORNEY OR AGENT REQUIRED			
Name (Print/Type)	Bret E. Field	Registration No.	97,620
Signature		Date	10-03-2001
Firm Name	Bozicevic, Field & Francis LLP	Address	200 Middlefield Road, Suite 200
City	Menlo Park	State	California
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		Facsimile	650-327-3231

Application No. 09/716,054 Attorney Docket No. STAN166 Page 2 of 2

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<div style="text-align: center;"> <p>COPY</p> <p>TRANSMITTAL</p> <p><input type="checkbox"/> Small Entity <input checked="" type="checkbox"/> Large Entity</p> </div>				Application Number		09/716,054	
				Confirmation Number		N/A	
				Filing Date		November 17, 2000	
				First Named Inventor		Crabtree	
				Examiner		Lisa V. Cook	
				Group Art		1641	
				Attorney Docket No.		STAN166	
ENCLOSED:		Claims	No. of claims as filed or other amendment	Most claims previously paid for	# Extra Claims	Rate	Totals
<input checked="" type="checkbox"/> Amendment Under Rule		Total	27	26	1	18	\$ 18.00
<input checked="" type="checkbox"/> 37 CFR § 1.111		Independent	3	3	0		\$ -
<input checked="" type="checkbox"/> Pages 18		Multiple					
				Total Extra Claim Fees			\$ 18.00
<input type="checkbox"/> Applicants Petition for an Extension of time from _____ to _____				A _____ month extension was previously filed and paid for thereby reducing the basic fee			
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<input type="checkbox"/> Filing Fee						Fee _____	
<input type="checkbox"/> Executed Declaration _____ Pages _____						Surcharge Fee _____	
<input type="checkbox"/> Other _____						Fee _____	
						Fee _____	
						Fee _____	
						Subtotal \$ -	
<input type="checkbox"/> Information Disclosure Statement							
<input type="checkbox"/> PTO Form 1449 _____ Pages _____							
<input type="checkbox"/> _____ Copies of Cited References							
<input type="checkbox"/> Other _____						Fee _____	
						Subtotal \$ -	
<input type="checkbox"/> Response to Notice to Comply (with copy of Notice to Comply)							
<input type="checkbox"/> Sequence Listing Certification							
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<input type="checkbox"/> Diskette in computer-readable format						Fee _____	
<input type="checkbox"/> Other _____							

<input type="checkbox"/> Terminal Disclaimer		Fees	
<input type="checkbox"/> Appeal to Board of Appeals and Appeal Communication to Group			
<input type="checkbox"/> Notice of Appeal	Pages		Fee
<input type="checkbox"/> Appeal Brief in Triplicate	Pages		Fee
<input type="checkbox"/> Reply Brief	Pages		Fee \$ -
			Subtotal \$ -
<input type="checkbox"/> Other Enclosures and/or Fees		Fee	
<input type="checkbox"/> Change of Correspondence Address		TOTAL FEES \$18.00	
<input checked="" type="checkbox"/> Return Receipt Postcard			
<p>The Commissioner is authorized to charge any fees which may be required, or credit any overpayment to Deposit Account 50-0815. If additional fees are required, including extensions of time, please consider this a petition therefore. A duplicate copy of this transmittal is enclosed.</p>			
SIGNATURE OF APPLICANT, ATTORNEY OR AGENT REQUIRED			
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Application No. 09/716,054

Attorney Docket No.

STAN186

Page

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of

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Typed or Printed Name	Donna Macedo	
Signature	<i>Donna Macedo</i>	Date 10/3/01
AMENDMENT UNDER 37 C.F.R. §1.111 RESPONSIVE TO PAPER NO. 11		
Address to: Assistant Commissioner for Patents Washington, D.C. 20231		
Attorney Docket Confirmation No.	STAN-166	
First Named Inventor	Crabtree	
Application Number	09/716,054	
Filing Date	November 17, 2000	
Group Art Unit	1641	
Examiner Name	Lisa V. Cook	
Title -	BIFUNCTIONAL MOLECULES AND THEIR USE IN THE DISRUPTION OF PROTEIN-PROTEIN INTERACTIONS	

Dear Sir:

This amendment is responsive to the Office Action dated July 3, 2001.

Please amend the above-identified application as follows.

In the Specification:

Page 6, please replace the paragraph beginning at line 30 and ending at page 7, line 3, with the following paragraph:

As such, the target protein ligand may be obtained from a library of naturally occurring or synthetic molecules, including a library of compounds produced through combinatorial means, i.e. a compound diversity combinatorial library. When obtained from such libraries, the target protein ligand employed will have demonstrated an affinity for its protein target in an appropriate screening assay for the activity. Combinatorial libraries, as well as methods for the production and screening, are known in the art and described in United States Patent Nos: 5,741,713; 5,734,018; 5,731,423; 5,721,099; 5,708,153; 5,698,673; 5,688,997; 5,688,696; 5,684,711; 5,641,862; 5,639,603; 5,593,853; 5,574,656; 5,571,698; 5,565,324; 5,549,974; 5,545,568;

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USSN: 09/716,034

5,541,061; 5,525,735; 5,463,564; 5,440,016; 5,438,119; 5,223,409, the disclosures of which are herein incorporated by reference.

Page 13, please replace the paragraph from lines 26 to 33 with the following:

Alternatively, the bifunctional inhibitor molecule can be produced using combinatorial methods to produce large libraries of potential bifunctional molecules which may then be screened for identification of a bifunctional molecule with the desired binding affinity and/or specificity. Methods for producing and screening combinatorial libraries of molecules include United States Patent Nos. 5,741,713; 5,734,018; 5,731,423; 5,721,099; 5,708,153; 5,698,673; 5,688,997; 5,688,696; 5,684,711; 5,641,862; 5,639,603; 5,593,853; 5,574,656; 5,571,698; 5,565,324; 5,549,974; 5,545,568; 5,541,061; 5,525,735; 5,463,564; 5,440,016; 5,438,119; 5,223,409, the disclosures of which are herein incorporated by reference.

In the Claims:

Cancel Claims 4 to 15.

16. (Amended) A method for inhibiting a binding event between a first target protein and a second binding protein in a host, said method comprising:

administering to said host an effective amount of a non-naturally occurring bifunctional inhibitor molecule of less than about 5000 daltons consisting of a target protein ligand bonded to a blocking protein ligand, optionally through a linking group, wherein said bifunctional inhibitor molecule is capable of simultaneously binding said target protein and said blocking protein in a manner sufficient to inhibit said binding event;

to produce a tripartite complex comprising said bifunctional inhibitor molecule, said target protein and said blocking protein that inhibits said binding event of said second binding protein to said first target protein.

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23. (Amended) The method according to Claim 22, wherein said blocking protein is selected from the group consisting of: peptidyl-prolyl isomerases, Hsp90 (Heat shock protein 90), steroid hormone receptors, cytoskeletal proteins, albumin and vitamin receptors.

Please enter the following new claims:

- 27. (New) A method for inhibiting a binding event between a first target protein and a second binding protein in a host, said method comprising:

administering to said host an effective amount of a non-naturally occurring bifunctional inhibitor molecule of less than about 5000 daltons consisting of a target protein ligand bonded to a blocking protein ligand through a linking group, wherein said bifunctional inhibitor molecule is capable of simultaneously binding said target protein and said blocking protein in a manner sufficient to inhibit said binding event, wherein said bifunctional inhibitor molecule is of the formula:



wherein:

X is target protein ligand;

L is a bond or a linking group; and

Z is different from X and is a blocking protein ligand;

to produce a tripartite complex comprising said bifunctional inhibitor molecule, said target protein and said blocking protein that inhibits said binding event of said second binding protein to said first target protein.

28. (New) The method according to Claim 27, wherein said bifunctional inhibitor molecule binds to a site of said target protein that is also bound by said second binding protein.

29. (New) The method according to Claim 27, wherein said bifunctional inhibitor molecule binds to a site of said target protein that is not bound by said second binding protein.

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30. (New) The method according to Claim 27, wherein said tripartite complex is produced intracellularly.
31. (New) The method according to Claim 27, wherein said tripartite complex is produced extracellularly.
32. (New) The method according to Claim 27, wherein said blocking protein is endogenous to said host.
33. (New) The method according to Claim 32, wherein said blocking protein is selected from the group consisting of: peptidyl-prolyl isomerases, Hsp90 (Heat shock protein 90), steroid hormone receptors, cytoskeletal proteins, albumin and vitamin receptors.
34. (New) The method according to Claim 27, wherein said bifunctional inhibitor molecule is administered as a pharmaceutical preparation.
35. (New) The method according to Claim 27, wherein X has a molecular weight of from about 50 to 2000 D.
36. (New) The method according to Claim 27, wherein said target protein is an extracellular protein.
37. (New) The method according to Claim 27, wherein said target protein is an intracellular protein.
38. (New) The method according to Claim 37, wherein said blocking protein is a peptidyl prolyl isomerase.
39. (New) The method according to Claim 27, wherein Z has substantially no pharmacologic

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activity apart from binding to a blocking protein. --

REMARKS

Following the above amendments, Claims 1-3, and 16-39 are pending, with Claims 1-3 and 25-26 being withdrawn from consideration.

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 16 to 24 and 27 to 39, the only claims pending and under examination at this time.

The specification has been amended to insert the phrase "United States Patent Nos." prior to the list of patent numbers at pages 6 and 13.

Claim 16 has been amended to specify that the molecules employed in the claimed methods are "non-naturally occurring," support for this amendment being found in the specification at page 4, lines 8-9. Claim 16 has also been amended to clarify that the target protein ligand is bound to the blocking protein ligand, where the target protein ligand may be directly bonded to the blocking protein ligand or bonded to the blocking protein ligand through a linking group, which linking group is optional. Support for this amendment can be found in the specification at page 4, lines 28 to 34, and elsewhere in the specification. Furthermore, the language of Claim 16 has been clarified to better state that the formation of the tripartite complex prevents the target protein from binding to the second binding protein. Finally, Hsp90 has been spelled out as Heat shock protein 90.

In addition, new Claims 27 to 39 have been added. These claims find support in originally pending Claims 16 to 24 and Claims 8 to 15.

Attached hereto is a marked up version of the changes made to the claims by the current

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amendment. The attached page is captioned "Version with Amendments to Claims
Made".

As can be seen from the above remarks and the attached copy of the marked up claims, no new matter has been introduced to the application by the above amendments. As such, the Examiner is respectfully requested to enter the above amendments.

With respect to the issue concerning the specification appearing on page 4 of the office action, this issue has been addressed through the above amendment.

Prior to addressing the remaining issues in the office action, it is believed that a brief review of the invention is helpful. The invention is directed to methods of inhibiting a protein-protein interaction in a host, e.g., for therapeutic purposes. In other words, the invention is directed to the field of inhibitor compounds for use in therapeutic applications. For example, the invention is directed to methods of inhibiting a biochemical event caused by two proteins, e.g., a target protein and an effector protein (which effector protein is referred to as a second binding protein in the above claims), by inhibiting the binding of the second protein to the target protein. Traditionally, such methods have been accomplished using inhibitor molecules. However, the size of the inhibitor molecule needed to provide for the blocking activity can be limiting with respect to practical use in therapeutic applications. As such, there has been an ongoing need in the field to identify small molecule inhibitors.

The present invention is based on the ingenious manner in which the inventors have satisfied this need for a small molecule effective inhibitor. In the present invention, a bifunctional molecule that recruits a blocking protein *in vivo* to produce an inhibiting complex is employed. The bifunctional molecule is made up of target protein ligand and a second ligand that binds to a blocking protein. When administered to the host, the bifunctional molecule binds to the target protein and a blocking protein, thereby inhibiting binding of the effector or second binding protein to the target. As the bifunctional ligand is a small molecule that nonetheless turns into an effective inhibitor complex when it binds to the blocking protein, it satisfies the above need felt in the field of pharmaceutical inhibitor active agents.

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TSSN: 09/716.034

See Exhibit A to this response which provides further illustration of the mechanism of action of the subject invention.

Turning now to the rejections presented in the Office Action, Claims 16-24 were rejected under 35 U.S.C. § 112, 2nd ¶ for a number of reasons. Each of these issues, i.e., issues A to G, is addressed separately below:

A. The Examiner asserts that the phrase "of less than about" in Claim 1 renders the claim indefinite because it is assertedly unclear whether the claim encompasses molecules that are less than 5000 daltons or less than or equal to 5000 daltons. It is respectfully submitted that the claim language is clear when read in view of the specification. The specification teaches at page 4, lines 24 to 27 that:

An important feature of the subject molecules is that they are small. As such, the molecular weight of the subject bifunctional inhibitor molecules is generally at least about 100 D, usually at least about 400 D and more usually at least about 500 D, and may be as great as 2000 D or greater, but usually does not exceed about 5000 D.

As such, when read in light of the specification, one would know that the claim covers the use of molecules that generally have a molecular weight that is less than or equal to 5000 D. However, one of skill in the art would also know that the claim covers the use of an equivalent small molecule that might slightly exceed about 5000 D in weight, so long as the molecule would still be considered small and not substantially different from molecules following within the literal range.

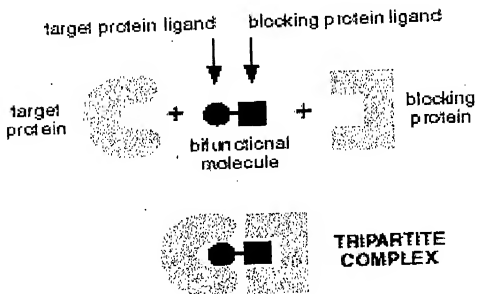
As such, the phrase "of at least about" does not render Claim 1 indefinite.

B. The Examiner asserts that the phrase "optionally joined" renders Claim 1 indefinite because it is assertedly not clear whether the two named ligands are always joined or in some embodiments not joined. It is believed that the amendment to Claim 1 clarifying that the target protein ligand is bonded to the blocking protein ligand, either directly or through an optional

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linking group, addresses this issue.

C. With respect to this issue, it is respectfully submitted that the Examiner is incorrectly equating the tripartite complex referenced in line 8 with the bifunctional molecule referenced in line 4. The bifunctional molecule is a single molecule that includes at least two moieties, i.e., the target protein ligand and the blocking protein ligand. The tripartite complex is produced when the target protein (distinct from the target protein ligand of the bifunctional molecule) and the blocking protein (distinct from the blocking protein ligand of the bifunctional molecule) bind to the bifunctional molecule, i.e., by binding to the target protein ligand and the blocking protein ligand, respectively, of the bifunctional molecule. The following illustration is believed to further clarify this point:



In view of the above explanation, it is submitted that this issue is addressed and resolved.

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D. With respect to this issue, Claim 16 now more specifically recites that the claim is directed to preventing a binding event between a first and second protein in a host, i.e., in vivo, and that the production of the tripartite complex caused by administering an effective amount of the bifunctional molecule causes this binding event to be prevented, i.e., by blocking access of the second protein to the first protein. It is respectfully submitted that there are no missing steps, and therefore this issue has been addressed.

E. With respect to this issue, it is submitted that as amended, Claim 16 clearly recites that the formation of the tripartite complex prevents the binding of the first and second proteins from occurring. The specification further clarifies that the tripartite complex prevents access of the second protein to its binding site on the target protein. Therefore, the claim is not indefinite when read in light of the specification.

F. In view of the above comments and the specification, it is clear that at no time will the bifunctional molecule and second binding protein (which can also be viewed as the effector protein as explained above) be able to bind the target protein at the same time at the same place. Furthermore, it is clear from the specification that the bifunctional molecule never binds to the second binding protein, just to the target protein and blocking protein. As such, this issue is addressed.

G. This issue is addressed through the above amendment to Claim 23.

In view of the above remarks and amendments to the claims, it is believed that all of the issues upon which the Examiner rejected the claims under 35 U.S.C. § 112, 2nd ¶ have been addressed and this rejection may be withdrawn.

The Examiner has also rejected claims 16-24 under 35 U.S.C. § 112, 2nd ¶ for the asserted reason that the claimed methods lack essential steps. This rejection appears to be based

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on the Examiner's erroneous conclusion that the claimed methods are directed to *in vitro* assays, e.g., *in vitro* screening assays to identify inhibitor compounds. However, as pointed out above, the claims are clearly directed to methods of inhibiting protein-protein interactions in a host for use in therapeutic applications. The claims are not directed to an *in vitro* assay to identify agents that inhibit the interaction of a first and second protein. As such, the claims do not omit any essential steps and this rejection may be withdrawn.

Claims 16 to 24 were next rejected to under 35 U.S.C. §102(b) as being anticipated by Griffith. In making this rejection, the Examiner equates FK506 with the bifunctional molecule employed in the subject claims. As amended, the bifunctional molecule employed in subject claims is a *non-naturally occurring* bifunctional molecule. Since FK506 is a naturally occurring molecule and the bifunctional molecule employed in the subject methods is a non-naturally occurring molecule, Griffith fails to teach the claimed methods and therefore does not anticipate the claimed methods. Accordingly, this rejection may be withdrawn.

Claims 16-21 and 24 were rejected under 35 U.S.C. §102 (b) as being anticipated by Varshavsky et al. This rejection is based on the Examiner's reading of Varshavsky as showing the production of tripartite complex in Figure 3, panels C and D on page 2097.

It is respectfully submitted that the Examiner is incorrectly reading the teaching of this particular Figure and Varshavsky in general. With respect to panels C and D of Figure 3, what is shown is a bifunctional molecule ($c-i^*$) that, in the absence of C binds to I (Panel C) but in the presence of C, does not bind to I (Panel D). Because binding to C prevents the bifunctional molecule from binding to I, at no point in the scheme depicted in Figure 3 is a tripartite complex of three distinct molecules produced. Instead, only binary complexes are produced, i.e., either I and the bifunctional molecule or C and the bifunctional molecule. Therefore, the scheme shown in this figure clearly does not anticipate Claims 16 to 24, as it clearly does not teach the production of a tripartite complex, much less one that prevents the binding of a target protein to a second binding protein.

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Viewed another way, the target protein in the scheme of Figure 3 is I, the bifunctional molecule is c-i* and the blocking protein is C. At no point in this scheme is a tripartite complex produced of I, c-i* and C. As such, at no point in this Figure does Varshavsky make a tripartite complex of a target protein, a bifunctional molecule and a blocking protein.

In fact, nowhere in the Varshavsky reference is the idea taught or suggested to make a tripartite complex of a target protein, a bifunctional molecule and blocking protein. Instead, all that is taught or suggested is binary complexes of either a bifunctional molecule and its target or a bifunctional molecule and a second protein that prevents the bifunctional molecule from binding to the target.

As such, Varshavsky fails to teach, or even suggest, a method in which a bifunctional molecule that produces a tripartite complex of itself, a target protein and a blocking protein is produced. Accordingly, Varshavsky fails to anticipate Claims 16-21 and 24 under 35 U.S.C. §102 (b) and this rejection may be withdrawn.

Finally, Claims 22 and 23 have been rejected under 35 U.S.C. § 103(a) over Varshavsky in view of Poulctty, for the asserted reason that Varshavsky teaches all of the elements of the claimed method but for the extracellular production of tripartite complexes, which element is assertedly made up by Poulctty.

However, as pointed out above, Varshavsky is fundamentally deficient in failing to teach or even suggest the production of tripartite complexes. In fact, Varshavsky actually teaches away from the production of tripartite complexes for the following reasons. Varshavsky's whole paper is directed to ways of making drugs more selective. The approach suggested is to link the drug to a second ligand that will bind to a protein in a cell where one does not want drug activity, such that when the bifunctional molecule binds to the second protein in the cell where drug activity is not wanted, the bifunctional molecule cannot bind to the drug target. As such, drug activity is limited to those cells that lack the second protein. For this scheme to work, binding to the second protein, i.e., the blocking protein, must prevent the bifunctional molecule from binding to the target. If the bifunctional molecule binds to the target, one would still get drug

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activity and selectivity would not be achieved. As such, Varshavsky's scheme only teaches if the bifunctional molecule cannot form a tripartite complex with a target protein and blocking protein.

This requirement of Varshavsky is directly opposite to the claimed methods, where one must produce a tripartite complex between a target protein, a bifunctional molecule and a blocking protein.

As such, Varshavsky teaches away from the claimed methods because Varshavsky teaches methods in which tripartite complexes must not be produced, but instead only binary complexes are produced. Because Varshavsky teaches away from methods in which tripartite complexes are produced, this reference fails to suggest the production of tripartite complexes, a required element of the claimed methods.

As Pouletty has been cited solely for the extracellular production site, the Pouletty teaching is incapable of making up the above fundamental deficiency in Varshavsky.

In sum, because the combined teaching of Varshavsky and Pouletty fails to teach or suggest, and in fact teaches away from, a method in which a tripartite complex of a bifunctional molecule, a target protein and blocking protein is produced, Claims 22 and 23 are not obvious over the combined teachings of these references and this rejection of Claims 22 and 23 under 35 U.S.C. § 103(a) over Varshavsky in view of Pouletty may be withdrawn.

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

Atty Dkt. No.: STAN166
USSN: 09/716,054

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: 10-3-01

By: Bret E. Field
Registration No. 37,620

encs:

Exhibit A

BOZICEVIC, FIELD & FRANCIS LLP
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F:\DOCUMENT\STAN (Stanford)\166\responses to first office action of 7-3-01.doc

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USSN: 09/716,054

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

As such, the target protein ligand may be obtained from a library of naturally occurring or synthetic molecules, including a library of compounds produced through combinatorial means, i.e. a compound diversity combinatorial library. When obtained from such libraries, the target protein ligand employed will have demonstrated an affinity for its protein target in an appropriate screening assay for the activity. Combinatorial libraries, as well as methods for the production and screening, are known in the art and described in United States Patent Nos: 5,741,713; 5,734,018; 5,731,423; 5,721,099; 5,708,153; 5,698,673; 5,688,997; 5,688,696; 5,684,711; 5,641,862; 5,639,603; 5,593,853; 5,574,656; 5,571,698; 5,565,324; 5,549,974; 5,545,568; 5,541,061; 5,525,735; 5,463,564; 5,440,016; 5,438,119; 5,223,409, the disclosures of which are herein incorporated by reference.

Page 13, please replace the paragraph from lines 26 to 33 with the following:

Alternatively, the bifunctional inhibitor molecule can be produced using combinatorial methods to produce large libraries of potential bifunctional molecules which may then be screened for identification of a bifunctional molecule with the desired binding affinity and/or specificity. Methods for producing and screening combinatorial libraries of molecules include United States Patent Nos: 5,741,713; 5,734,018; 5,731,423; 5,721,099; 5,708,153; 5,698,673; 5,688,997; 5,688,696; 5,684,711; 5,641,862; 5,639,603; 5,593,853; 5,574,656; 5,571,698; 5,565,324; 5,549,974; 5,545,568; 5,541,061; 5,525,735; 5,463,564; 5,440,016; 5,438,119; 5,223,409, the disclosures of which are herein incorporated by reference.

In the Claims:

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Cancel Claims 4 to 15.

16. (Amended) A method for inhibiting a binding event between a first target protein and a second binding protein in a host, said method comprising:

administering to said host an effective amount of a non-naturally occurring bifunctional inhibitor molecule of less than about 5000 daltons consisting of a target protein ligand and bonded to a blocking protein ligand, optionally joined by through a linking group, wherein said bifunctional inhibitor molecule is capable of simultaneously binding said target protein and said blocking protein in a manner sufficient to inhibit said binding event;

whereby to produce a tripartite complex comprising said bifunctional inhibitor molecule, said target protein and said blocking protein ~~is produced that inhibits~~ that inhibits said binding event of said second binding protein to said first target protein.

23. (Amended) The method according to Claim 22, wherein said blocking protein is selected from the group consisting of: peptidyl-prolyl isomerases, Hsp90 (Heat shock protein 90), steroid hormone receptors, cytoskeletal proteins, albumin and vitamin receptors.

Please enter the following new claims:

--27. (new) A method for inhibiting a binding event between a first target protein and a second binding protein in a host, said method comprising:

administering to said host an effective amount of a non-naturally occurring bifunctional inhibitor molecule of less than about 5000 daltons consisting of a target protein ligand bonded to a blocking protein ligand through a linking group, wherein said bifunctional inhibitor molecule is capable of simultaneously binding said target protein and said blocking protein in a manner sufficient to inhibit said binding event, wherein said bifunctional inhibitor molecule is of the formula:

Z-1.-X

wherein:

X is target protein ligand;

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I. is a bond or a linking group; and

Z is different from X and is a blocking protein ligand;

to produce a tripartite complex comprising said bifunctional inhibitor molecule, said target protein and said blocking protein that inhibits said binding event of said second binding protein to said first target protein.

28. (New) The method according to Claim 27, wherein said bifunctional inhibitor molecule binds to a site of said target protein that is also bound by said second binding protein.

29. (New) The method according to Claim 27, wherein said bifunctional inhibitor molecule binds to a site of said target protein that is not bound by said second binding protein.

30. (New) The method according to Claim 27, wherein said tripartite complex is produced intracellularly.

31. (New) The method according to Claim 27, wherein said tripartite complex is produced extracellularly.

32. (New) The method according to Claim 27, wherein said blocking protein is endogenous to said host.

33. (New) The method according to Claim 32, wherein said blocking protein is selected from the group consisting of: peptidyl-prolyl isomerases, Hsp90 (Heat shock protein 90), steroid hormone receptors, cytoskeletal proteins, albumin and vitamin receptors.

34. (New) The method according to Claim 27, wherein said bifunctional inhibitor molecule is administered as a pharmaceutical preparation.

35. (New) The method according to Claim 27, wherein X has a molecular weight of from

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about 50 to 2000 D.

36. (New) The method according to Claim 27, wherein said target protein is an extracellular protein.
37. (New) The method according to Claim 27, wherein said target protein is an intracellular protein.
38. (New) The method according to Claim 37, wherein said blocking protein is a peptidyl prolyl isomerase.
39. (New) The method according to Claim 27, wherein Z has substantially no pharmacologic activity apart from binding to a blocking protein. --

EXHIBIT A

Bifunctional molecules and their use in

Challenge: Inhibit the interaction of the target with its substrate or protein partner

Solution:

